

**REMARKS/ARGUMENTS**

The above amendments have been provided based on the format described at 1265 Off. Gaz. Pat. Office 87 (December 17, 2002) and as authorized by Deputy Commissioner for Patents, Stephen Kunin on January 31, 2003.

Claim 20 has been amended to introduce the formulas from Figures 1-1 and 1-2 as recited in the claims. The formulas in the claim utilize a different means of depicting the hydro-monobenzoporphyrin (Gp) structures represented by the formulas, and formulas 2, 4, and 6 have been corrected to remove a pentavalent carbon atom which was erroneously present in the Figures as filed. The scope of the claim, and claims that depend from claim 20, have not been altered.

Support for the formulas is provided by the Figures and application as originally filed. No new matter has been introduced, and entry of the amendment is respectfully requested.

***Rejection under 35 U.S.C. § 112, second paragraph***

Claims 20-25 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for failure of claim 15 to provide antecedent basis for the recited formulas. Claim 20, from which claims 21-25 depend, refers to both claim 15 and to Figures 1-1 and 1-2. It is Figures 1-1 and 1-2 which provide the formulas in question. Therefore, claim 20 has been amended to expressly recite the formulas as discussed above. Withdrawal of the instant rejection is respectfully requested.

***Rejection under obviousness-type double patenting***

Claims 15-34 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-12 of U.S. Patent 6,074,666. Applicants thank the Examiner for maintaining the rejection in abeyance pending a notification of allowable claims.

***Rejection under 35 U.S.C. § 102(e)***

Claims 15-20 and 30-34 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Madden (USP 5,389,378). Applicants have carefully reviewed the statement of the rejection and traverse as follows. As an initial matter, Applicants' previous discussion of sugars as recited in the claims was in the context of the sugars contributing to the osmolarity of the liposomes in the claimed compositions.

Madden is alleged to disclose liposome formulations that are "isotonic (meaning that the osmolarity is the same as blood)."

As an initial matter, Applicants point out that the sole discussion of "isotonic" formulations in Madden is in column 10, lines 27-30, which state as follows

For parenteral administration, the liposomes may best be used in the form of a sterile aqueous solution which may contain other solutes, for example, sufficient salts, glucose or dextrose to make the solution isotonic.

Therefore, Madden discusses that the solution in which his liposomes may be used is isotonic. There is no discussion as to the osmolarity of the liposomes.

The instant claims, however, recite that the claimed formulations comprise liposomes that have the osmolarity of human blood. Applicants respectfully point out that tonicity and osmolarity are two distinct concepts. Tonicity, as used by Madden and in the art, is consistently a **relative** term that depends on the nature of a solution's solutes and their concentrations. The solutes are of two types with respect to tonicity: solutes that penetrate a semi-permeable lipid bilayer and solutes that do not penetrate such a bilayer.

Tonicity describes the net movement of water through a semi-permeable lipid bilayer, such as the movement of water from a solution into a cell, or liposome, in contact with said solution.

If water moves from the solution into a cell, the solution is said to be hypotonic. If water moves from the cell into the solution, the solution is said to be hypertonic. If there is no net movement of water between the solution and the cell, the solution is said to be isotonic.

Because tonicity is a **relative** term, however, it is unclear what Madden's solution as quoted above is "isotonic" to. Is Madden's solution isotonic relative to Madden's liposomes, or some cell of a subject to be treated with the parenteral solution containing said liposomes, or something else? In the first possibility, if Madden's solution is isotonic relative to Madden's liposomes, it says nothing about the osmolarity of Madden's liposomes because those liposomes do not necessarily have the same osmolarity of human blood. In the second possibility, if Madden's solution is isotonic relative to cells that may be parenterally contacted with the solution, it also says nothing about the osmolarity of Madden's liposomes which do not have to have the same osmolarity as such cells. Therefore, and in either case, Madden's liposomes do not necessarily have the osmolarity of human blood to anticipate the instant claims.

The above follows from the fact that osmolarity is defined as the number of particles per liter of solution and is expressed as osmoles per liter. Therefore, and based upon the first possibility above, the use of a solution that is "isotonic" for liposomes contained therein only means that there is no net movement of water between the solution and the liposomes. The liposomes do not necessarily have the osmolarity of human blood because the liposomes can have more or less particles per liter of solution than human blood.

Similarly, and based upon the second possibility above, the placement of liposomes in a solution that is "isotonic" for some cells in a physiological setting only means that there is no net movement of water between the solution and such cells. There is no information regarding the osmolarity of the liposomes, which again can be significantly higher or lower than that of human blood. In this possibility, Madden's solution may still be hypotonic or hypertonic relative to his liposomes.

The instant claims define the liposomes as having the osmolarity of human blood, which is not disclosed by Madden for the reasons provided above. As discussed above, tonicity provides

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no information about osmolarity because tonicity is a **relative** term defined upon the net movement of water between a solution and a lipid bilayer defined entity. Therefore, and contrary to the Examiner's assertion that Madden's disclosure of an isotonic solution means that "the osmolarity is the same as blood", Applicants respectfully submit that Madden does not provide any disclosure of formulations comprising liposomes having the osmolarity of human blood. Accordingly, Madden cannot anticipate the instant claims, and withdrawal of the instant rejection is respectfully requested.

***Rejection under 35 U.S.C. § 103(a)***

Claims 26, 27, 33 and 34 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Madden (USP 5,389,378). Applicants have carefully reviewed the references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

As noted above, Madden does not teach, suggest, or otherwise indicate liposomes having the osmolarity of human blood, and so does not teach formulations comprising such liposomes. Therefore, and contrary to the statement of the rejection, it cannot have been obvious to adjust the amounts of sugar as recited in claims 26, 27, 33 and 34 such that the resultant liposomes would have the osmolarity of human blood. Accordingly, the instant rejection may be properly withdrawn.

Claims 28 and 29 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Madden (USP 5,389,378) in view of Barenholz (USP 4,797,828). Applicants have carefully reviewed the references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

Barenholz is asserted as disclosing the use of antioxidants in liposomes. However, Barenholz fails to remedy the critical deficiency of Madden's failure (as noted above) to disclose liposomes having the osmolarity of human blood. In light of this deficiency, Applicants respectfully

submit that the claimed subject matter cannot have been obvious at the time of the invention and that this rejection may be properly withdrawn.

Claims 20-25 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Madden (USP 5,389,378) in view of Applicant's statements. Applicants have carefully reviewed the references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

As an initial matter, Applicants point out that the statement of the rejection refers to Thompson and Kappas in addition to Madden. Applicants believe that the inclusion of Thompson and Kappas is a clerical error because claims 20-25 are rejected over these references on pages 7-8 of the Office Action.

The statement of the rejection alleges that because the porphyrin derivatives recited in the claims are known in the art, it would have been obvious to use them in the liposomes of Madden. Without acquiescence to whether such an allegation is correct, Applicants respectfully point out that because Madden fails to teach all the limitations of claims 20-25 (as discussed above), it is not possible for Madden to render the claims obvious in light of any Applicant statements concerning porphyrin derivatives. Accordingly, no case of obviousness is presented, and the instant rejection may be properly withdrawn.

Claims 15-20 and 25-34 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Thompson et al. (USP 5,277,913) or Kappas et al. (USP 5,010,073) individually in view of Crowe et al. (USP 4,857,319), further in view of Madden (USP 5,389,378). Applicants have carefully reviewed the references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

The statement of the rejection acknowledges that neither Thompson or Kappas teach liposomal formulations that comprise sugar and that Crowe teaches the inclusion of sugar to protect liposomes during dehydration and rehydration. The statement of the rejection further asserts that it would have been obvious to adjust the amount of salts, glucose or dextrose in the liposomes of Thompson or Kappas in light of Crowe to result in isotonic formulations.

Without acquiescence to whether the above allegation is correct, Applicants respectfully point out that, as discussed above, producing an isotonic parenteral solution as provided by Madden does not necessarily mean the production of liposomes having the osmolarity of human blood. In light of this deficiency, no case of obviousness is presented, and the instant rejection may be properly withdrawn.

Claims 28 and 29 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Thompson et al. (USP 5,277,913) or Kappas et al. (USP 5,010,073) individually in view of Crowe et al. (USP 4,857,319) and Madden (USP 5,389,378) and Barenholz (USP 4,797,285). Applicants have carefully reviewed the references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

As with the rejection based in part on the above rejections based in part on Thompson et al. or Kappas et al. individually in view of Crowe et al., and based in part on Barenholz, none of the references discloses liposomes having the osmolarity of human blood. Therefore, not all of the limitations of claims 28 and 29 have been met, and Applicants respectfully request that this rejection may be withdrawn.

Claims 20-25 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Madden (USP 5,389,378) or Thompson et al. (USP 5,277,913) or Kappas et al. (USP 5,010,073) individually in view of Crowe et al. (USP 4,857,319). Applicants have carefully reviewed the

references and the statement of the rejection and respectfully traverse because no *prima facie* case of obviousness has been presented.

As with the obviousness rejection of claims 20-25 above in light of Madden alone, and again without acquiescence to whether it would have been obvious to use known porphyrin derivatives in the liposomes of Thompson et al. or Kappas et al. in view of Crowe et al., Applicants respectfully point out that because Madden fails to teach or suggest liposomes having the osmolarity of human blood as discussed above, it is not possible for Madden to render obvious the modification of any other liposome to have the osmolarity of human blood. Accordingly, no case of obviousness is presented, and the instant rejection may be properly withdrawn.

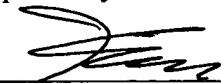
### Conclusion

In light of the above discussion, Applicants respectfully submit that the claims are allowable, and passage of the application to issue is urged. The Examiner is welcome to contact the undersigned to resolve any residual issues, such as the submission of a terminal disclaimer, or if further discussions may be thought useful.

In the event that the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 273012008102. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By   
Kawai Lau, Ph.D.

Registration No.: 44,461  
MORRISON & FOERSTER LLP  
3811 Valley Centre, Suite 500  
San Diego, California 92130  
(858) 720-5100  
Attorneys for Applicant